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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/699,550	10/31/2003	Susan J. Wong	454311-2232.1	9527

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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
MCGAW, MICHAEL M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/699,550	WONG ET AL.	
	Examiner	Art Unit	
	Michael M. McGaw	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-161* is/are pending in the application.

4a) Of the above claim(s) *1-73,106-125,129-144,146-155 and 157-161* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74-105,126-128,145 and 156* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group VII, claims 74, 78-105, 126-128 and 145, in the reply filed on July 30, 2004 is acknowledged. Claims 75, 78, 79, 105 and 156 are rejoined for reasons indicated below. Furthermore, claims 76 and 77 should have been included in Group VIII. As Group VIII is being rejoined, claims 76 and 77 will be rejoined as well. Thus, claims 74-105, 126-128, 145 and 156 are currently under examination.

Claims 1-68, 106-125, 129-144, 146-155, 157-161 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse ***with respect to these claims*** in the reply filed on July 30, 2004.

Claims 69-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction requirement in the reply filed on July 30, 2004.

Applicant has requested that Groups VI (claims 69-73), VIII (claims 75, 78, 79, and 105) and XVI (claim 156) be searched and examined together in this application. The traversal is on the ground(s) that a search of the claims in Group VII will involve a search of Groups VI, VIII and XVI. This is found persuasive with respect to Groups VIII and XVI. This is not found persuasive with respect to Group VI because the claims of

Group VI read on an isolated NS5 protein. Thus, the search for these claims is not coextensive with the search for the claims of the groups currently under examination. If the claims of Group VI are amended to include some definite immunoassay ingredients, thus narrowing their scope, rejoinder of those claims for examination in the present application would be appropriate.

It appears that the traversal relates solely to the Groups mentioned immediately above (i.e. Groups VI-VIII and XVI) and that applicant is not traversing the restriction requirement as it relates to the remaining groups. In the interest of clarity, the examiner points out, as does applicant on page 33 of the correspondence dated July 30, 2004, that the Groups above are related in that they are all drawn to methods and kits utilizing WNV NS5. The remaining groups do not utilize NS5. Thus, these groups require a different field of search.

Claims 69-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The restriction requirement (with the rejoinder of Groups VIII and XVI) is still deemed proper and is therefore made FINAL.

Priority

This application claims the benefit of both 60/422,755 filed on October 31, 2002 and 60/476,513 filed on June 6, 2003. Applicant has elected to prosecute claims relating to a method for detecting WNV infection using NS5. It appears to the examiner

that support for this invention dates back solely to the 60/476,513 application filed on June 6, 2003.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the citizenship of each inventor.

Claim Rejections - 35 USC § 112, ¶2

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 75-79, 89-91, 94, 105, 126-128, 145 and 156 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 75 states in relevant part "comprising ***a WNV NS5 protein*** or an immunogenic fragment thereof whereby ***the E glycoprotein*** or the immunogenic fragment thereof having a native conformation or non-denatured structure is specifically reactive..." The claim refers to both the NS5 protein and the E glycoprotein, where the reference to E glycoprotein lacks antecedent basis. In the interest of compact prosecution, the claim is being interpreted as follows: "comprising ***a WNV NS5 protein*** or an immunogenic fragment thereof whereby ***the WNV NS5 protein*** or the

immunogenic fragment thereof having a native conformation or non-denatured structure is specifically reactive..." Appropriate correction is required.

Claims 75-79 are further rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Claim 75 is directed to a method of detecting a protective immune response. The only step involves contacting a biological sample with the WNV NS5 antigen. There is no step whereby the complex formed between the WNV NS5 and the biological sample is detected. Therefore, it is not clear how this method "detects" the immune response.

Claim 77 refers to "the amino acid sequence of the WNV NS5 protein or fragment thereof is the amino acid sequence encoded by the NS5 protein encoding DNA sequence of Genbank accession No. AF 404756, or a fragment thereof." Somewhat analogous to the situation with trademarks where the owner of a mark such as Coca-Cola can revise a formulation, Genbank accession numbers are considered indefinite because that which is defined by them, the underlying sequence, can change over time due to events such as revisions. Again, the examiner suggests referencing a particular SEQ ID NO, assuming the sequence has been submitted, rather than the Genbank number.

Additionally, claim 77 states in relevant part "the amino acid sequence encoded by the NS5 protein encoding DNA sequence of..." This line does not make sense. How does the NS5 protein encode a DNA sequence? Doesn't a DNA sequence encode a

protein and not the other way around? Likewise, the NS5 protein does not encode an amino acid sequence.

Claims 78, 89, 90 indicate that the protein of fragment is part of a fusion protein. This is incompatible with the limitation that the WNV NS5 protein or immunogenic fragment thereof has a native conformation or non-denatured structure. Once you fuse the entire protein to something else it cannot have either a native conformation or a non-denatured structure. See also the § 112, ¶1 section below relating to a rejection of claims 74 and 75 and the terminology "native conformation or non-denatured structure."

Claim 90 refers to "WNV NS5 or subfragment there of." What is a subfragment of WNV NS5? How is a subfragment different than a fragment of WNV NS5?

Claim 105 provides for the "method for the transfer of information obtained as a result of carrying out the methods of any of claims 74, 75, 80, 91, or 99", but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 126-128 claim "[a] method for rapidly detecting anti-WNV antibody..." or "rapidly determining..." Rapidly is a relative term. Relative to what is this rapid?

Claims 145 and 156 are being considered as including the limitations of the withdrawn independent claims 144 and 150, respectively, from which they depend. As such, they would include the terminology "rapidly". Also, they would include the relative term "recent". What are the bounds of a "recent" infection?

Claims 91, 94, 126-128 use the phrase "increase reaction kinetics". Again, the term "increase" is a relative term. This is an increase of reaction kinetics relative to what?

Claim Rejections - 35 USC § 112, ¶1

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 74-104, 126-128, 145 and 156 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection involves several aspects.

I. "not detectably cross-reactive"

Claim 74 indicates that "the NS5 the NS5 protein or the immunogenic fragment thereof is specifically reactive with anti-WNV antibodies but ***not detectably cross-reactive*** with antibodies against a flavivirus other than WNV..." (emphasis added) Independent claims 75, 80, 91, 99, 126, 127, 128 use similar language. Applicant defines "detectably cross-reactive" on page 29 of the specification as follows:

> As it is used herein, the phrase "detectably cross-reactive" is meant to refer to an antigen-antibody interaction that can be substantiated by measuring or detecting a binding complex formed from the interaction between the antigen and antibody. Thus, the recitation "not substantially or detectably cross-reactive" is meant to

exclude antigen-antibody interactions that are non-specific, i.e. background 'noise".

As a preface, to say that something is not "substantially or detectably cross-reactive" is not the same as saying that something is not "detectably cross-reactive." The phrase detectably cross-reactive is a fairly objective statement; either it is cross-reactive or it is not. The phrase "substantially cross-reactive" is far more subjective. It is much more likely that reasonable persons could differ on the boundaries of such a term.

Figure 26 details the cross-reactivity between WNV NS5 and sera from patients infected with DENV. The text on page 36 indicates that "only 8.8% of the total dengue patient sera showed a cross-reaction with the WNV NS5 antigen..." Thus, NS5, by applicants own statement, is cross-reactive with antibody raised against other flavivruses. Clearly this is detectable. Thus, WNV NS5 ***is*** detectably cross-reactive with antibody raised against DENV. Whether these interactions are non-specific is difficult to say, but at 8.8% it is somewhat irrelevant whether or not it is specific; it is still detectably cross-reactive.

Furthermore, it is known that "primary responders exhibit mainly monotypic antibody responses, but with successive infections, the antibody response broadens to include heterotypic reactivity to other flaviviruses in the same or different antigenic groups" leading to the conclusion that both the occurrence and the specificity of cross reactivity increases with subsequent exposures to flaviviruses. Tardei, et al., (2000) J. Clin. Microbiol. Vol. 38, No. 6, pp 2232-2239, 2234. It seems quite plausible that the 8.8% responders in the group were secondary responders with specific reactions to the

NS5. This quite likely explains why there was a greater cross-reactivity with DENV than with SLE. Various DENV serotypes are known to co-circulate in areas where the virus is endemic. Also, in areas where DENV is endemic, other flavivruses also are present. In the Carribean basin DENV overlaps YF virus. In Asia DENV overlaps JEV. Hepatitis C is also present in these areas. Thus, there is potential for repeat exposure to flavivruses. In contrast, SLE tends to circulate in the southeastern US, such as Texas and the lower Mississippi River area where repeat exposure to flavivruses is not as likely. This could certainly explain why the cross-reactivity to DENV was higher than SLE.

II. "against a flavivirus other than WNV"

Claims 74-104, 126-128 and 145 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being ***potentially*** enabling for a phrase such as "against SLE or DENV", does not reasonably provide enablement for "against a flavivirus other than WNV". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The data presented disclose the cross-reactivity between WNV NS5 and sera from patients with DENV or SLEV. The family Flavivirdae comprises 69 viruses, 38 of which are associated with human disease. One cannot extrapolate across the whole flavivirus family based upon results from only DENV and SLE cross-reactivity studies. As a critical issue, based on E protein homology WNV is more closely related to JEV than to SLE. See Monath, TP et al., *Flaviviruses*. In: Fields Virology, 3rd Edition. (1996)

pg. 961, Fig. 2. JEV is very significant human pathogen in Asia. Based upon this homology, one would want to know, at a minimum, whether WNV NS5 antigen was cross-reactive with sera from patients with JEV before asserting that WNV NS5 is not cross-reactive with antibody against a flavivirus other than WNV. To really make a valid assertion that WNV NS5 is not cross-reactive with other flavivruses one would need to present such data from a broader cross-section of flavivruses, not limited to just DENV, JEV and SLE.

As an academic matter, it would be interesting to know if someone suffering a chronic Hepatitis C (HCV) infection cross-reacts with antigen to WNV NS5. Such patients are known to mount a fairly strong response to HCV NS5. See for instance Chien, DY et al. (1992) *PNAS*, vol. 89, pp. 10011-10015.

III. "protective immune response"

Claims 75 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 75 is directed to "[a] method for detecting a protective immune response in a subject..." which further indicates that one is using an NS5 antigen that is "specifically reactive with protective antibodies against WNV..." Use of the word "protective" raises a number of issues.

First, how does one know that NS5 is "specifically" reactive with **protective** antibodies? How do we know that it does not also react with non-protective antibodies? For instance, if we say that NS5 reacts with a given set of antibodies, that set would be the union of two subsets; protective antibodies and non-protective antibodies. It is unlikely that the subset of non-protective antibodies would be an empty set while the subset of protective antibodies is coextensive with the entire set of antibodies reactive with NS5. Thus, NS5 is not expected to be specifically reactive with protective antibodies.

Second, it does not appear that anyone has ever shown that antibody against WNV NS5 is, in fact, protective. NS 5 is a nonstructural protein. While antibody against the E glycoprotein ***might*** be protective, as neutralizing antibody, it is not immediately evident that antibody against a nonstructural protein would be similarly neutralizing. Thus, NS5 antibodies would not be "protective antibodies against WNV."

Lastly, where one is looking at acute phase sera, the mere detection of antibody at such an early stage would not necessarily be indicative of a protective immune response. Even if one detected antibody against E, one could not be certain the patient would survive.

Likewise, the final line of claims 74 and 75 indicates there is "no detectable cross-reactivity with protective antibodies against a flavivirus other than WNV." This does not rule out cross-reactivity with non-protective antibodies such as antibodies against Dengue NS5 does it?

IV. "having native conformation or non-denatured structure"

Claims 74, 75, 80, 91, 99, 126, 127, 128 (as does claim 145 when rewritten in light of withdrawn claim 144) recite in part that "whereby the WNV NS5 protein or the immunogenic fragment thereof ***having a native conformation or non-denatured structure***..." While one can envision that an isolated protein might retain a native conformation or non-denatured structure, the same cannot be said of an immunogenic fragment. To say that a protein is native indicates that its primary, secondary and tertiary structure is maintained. The term "denatured" similarly defined. Stedman's Medical dictionary 27th Edition defines denatured as "made unnatural or changed from the normal in any of its characteristics..." Clearly the process of making a fragment causes the resulting protein to be unnatural and may likely result in a loss of its normal characteristics. Considering that the antigenicity and specific reactivity of the WNV NS5 is due in part to conformational epitopes; considering that these conformational epitopes frequently involve non-contiguous residues/regions which are juxtaposed by the three-dimensional folding of the protein; considering the unpredictable effects of any deletion upon folding; considering the uncharacterized nature of the epitopes involved in reproducing the antigenicity of the entire native protein; considering the quantity of experimentation, the lack of guidance, and the lack of working examples, it is maintained that undue experimentation would be required to enable the claimed fragments reproducing the antigenicity of the native WNV NS5 protein.

V. Use of NS5 to detect flavivrus infection.

Claim 156 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detecting a WNV infection using WNV NS5 antigen, does not reasonably provide enablement for detecting a flavivirus infection using a WNV infection. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claim 156 is an elected dependent claim. It depends upon withdrawn claim 150. If claim 156 were rewritten to include the limitations of claim 150 the result would essentially be an immunochromatographic test for rapidly detecting a flavivirus infection using WNV NS5. As mentioned elsewhere, WNV is one of 69 flaviviruses. To the extent there are no cross-specific reactions with WNV NS5 antigen such a test would be ineffective against a flavivirus other than WNV.

VI. Other 112, first paragraph issues.

Claim 76 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In particular, claim 76 is directed to "[t]he method as in one of claims 74-75, wherein said NS5 protein or fragment thereof is from WNV isolate 2741."

These claims require the use of specific biological materials, in particular, isolate 2741. As a required element of enablement such biological material must be known and readily available to the public or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by the deposit of the strains recited in the claims. See CFR 1.802. The specification does not provide a repeatable method for obtaining these strains and it is not apparent that they are readily available the public.

It appears that NS5 of WNV isolate 2741 has a known amino acid. As an alternative to deposit, applicant can fulfill the enablement requirement by teaching the particular sequence. For instance, reference to a particular SEQ ID NO in the claim would alleviate the problem and would be preferable.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 105 is rejected under 35 U.S.C. 101 because the claimed recitation of a method, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

See also MPEP §2106 pg. 2100-18 rev. 2, May 2004:

> For such subject matter to be statutory, the claimed process must be limited to a practical application of the abstract idea or mathematical algorithm in the technological arts. See Alappat, 33 F.3d at 1543, 31 USPQ2d at 1556-57 (quoting Diamond v. Diehr, 450 U.S. at 192, 209 USPQ at 10). See also Alappat 33 F.3d at 1569, 31 USPQ2d at 1578-79 (Newman, J., concurring) ("unpatentability of the principle does not defeat patentability of its practical applications") (citing O 'Reilly v. Morse, 56 U.S. (15 How.) at 114-19). A claim is limited to a practical application when the method, as claimed, produces a concrete, tangible and useful result; i.e., the method recites a step or act of producing something that is concrete, tangible and useful. See AT &T, 172 F.3d at 1358, 50 USPQ2d at 1452.

The method of claim 105 does not recite a step or act of producing something that is concrete, tangible and useful.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 74, 76-82, 85-90 and 126-128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang, T. et al. in view of Valdes, K. et al.

Applicant claims a method of detecting WNV infection using a WNV NS5 protein where the NS5 is specifically reactive with anti-WNV antibody but not detectably cross-reactive with antibodies against a flavivirus other than WNV. See independent claims 74, 80, 126-128.

Wang, T. et al (2002) Vector Borne and Zoonotic Diseases 2(2) pp. 105-109 teach a method of detecting WNV infection using a WNV E protein. Wang indicates that sera

from patients with other flaviviral infections, including dengue, JEV, and yellow fever, did not yield positive results in the ELISA, indicating that the ELISA with recombinant E protein may be specific for West Nile virus infection (page 108). Wang used WNV isolate 2741 (see page 106). Wang's WNV E protein was prepared as a recombinant fusion protein with maltose binding protein. Wang performed both immunoblots and ELISAs to confirm the efficacy of their assays. Wang indicated that the ELISA could be performed more rapidly than the immunoblot as the immunoblot was laborious (see page 109). Wang indicates that the E protein reacted with IgM and was also reactive with sera from patients at approximately 3 weeks post-infection (see page 107). Thus, Wang was able to detect a recent or ongoing WNV infection. Wang used systems involving a second antibody. The second antibody was coupled to alkaline phosphatase (see page 106).

Valdes, K, et al. (2000) Clinical and Diagnostic Laboratory Immunology 7(5) 856-857 teach a method for detecting dengue, a related flavivirus, using dengue E and NS5 antigens. Valdes indicates a "wide antibody response to NS5 protein (similar to E)..." (page 856, col. 2, last full paragraph).

Given that Wang has shown that E protein is specific for WNV infection; given that the E protein of a flavivirus may be slightly more immunogenic than NS5; given that the presence of circulating antibody to E lasts for a greater duration the antibody to NS5; one could conclude that by combining the teachings of Wang and Valdes one would yield a method of detecting WNV infection using a WNV NS5 protein where the NS-5 is specifically reactive with anti-WNV antibody but not detectably cross-reactive

with antibodies against a flavivirus other than WNV. Thus, one of ordinary skill in the art would have been motivated to combine the teachings of Wang and Valdes because Wang teaches methods of detecting WNV infection using E antigen while Valdes teaches that methods applicable to the E antigen of a flavivirus are also applicable to the NS5 antigen. One of ordinary skill in the art would have expected to achieve a method of detecting WNV infection using a WNV NS5 protein where the NS-5 is specifically reactive with anti-WNV antibody but not detectably cross-reactive with antibodies against a flavivirus other than WNV as outlined above. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 83-84, 91-104, 145 and 156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang, T. et al. in view of Valdes, K. et al. as applied to claims 74, 76-82, 85-90 and 126-128 above, and further in view of Mandy, F. et al.

Independent claims 90, 99, 145 (if rewritten in light of claim 144), as well as many of the dependent claims, involve the application of previously described techniques of microsphere immunoassay, as taught by Mandy, FF, et al. Overview and application of suspension array technology (2001) Clinics in Laboratory Medicine. Vol. 21, pp. 713-729, to the subject matter of aforementioned claims 74 and 80. Mandy indicates that "the functional modules for the SAT are the same as for radioimmunoassay or the enzyme-linked immunosorbent assay (ELISA)". (see page 713) Thus, the skilled practitioner would know that SAT technology could be

interchanged with detection by ELISA to perform an immunoassay. Mandy teaches a microsphere coupled to a bead and also teaches a second antibody as a reporter. (See Figs. 1 & 2 and pgs. 714-15).

Mandy indicates that SAT "can be constructed as a direct or an indirect method depending upon the nature of the attachment of the fluorochromes to the reporter molecules." And as to reaction kinetics, "[t]he quality of the Mabs, the level of the sensitivity required, the level of the suspension agitation available, and selected temperature all contribute to the duration of incubation, with anticipated ranges for incubations from 15 minutes to 2 hours." (See page 725). Mandy teaches that the techniques are applicable to biological samples such as bodily fluids in volumes as small as 10-20 microliters. (pg. 724).

One of ordinary skill in the art would have been motivated to combine the teachings of Wang, T. et al. in view of Valdes, K. et al. with that of Mandy et al because Mandy teaches that immunoassays which can be performed using techniques such as ELISAs can also be performed by SAT techniques involving microspheres. One of ordinary skill in the art would have expected to achieve an immunoassay which was quicker to perform, had a higher throughput, involved very small sample sizes, etc. because Mandy teaches these benefits through application of microsphere immunoassays. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

Claims 74-105, 126-128, 145 and 156 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-9, 13-21, 24-35 and 56-57 of copending Application No. 10/839,442. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed a method of detecting WNV infection in a subject using flavivrus molecules with specificity towards NS5. This is a ***provisional*** double patenting rejection since the conflicting claims have not yet been patented.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Chien, DY et al. (1992) *PNAS*, vol. 89, pp. 10011-10015, teach the use of NS5 antigen in the detection of anti-HCV antibody. Subsequent publications by Chien, including Chien, DY et al (1999) J. Clin. Microbiol. Vol. 37(5) pp. 1393-1397, include the use of NS5 in fusion proteins. Davis, B.S. et al (2001) Journal of Virology, 75(9) 4040-4047, teach serologic detection of WNV infection using PrM-E antigens.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Wednesday, September 08, 2004

MARY E. MOSHER
PRIMARY EXAMINER
GROUP 1800 1600